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IUGA GRAFTS ROUNDTABLE 2010

# A standardized description of graft-containing meshes and recommended steps before the introduction of medical devices for prolapse surgery

## Consensus of the 2nd IUGA Grafts Roundtable: Optimizing Safety and Appropriateness of Graft Use in Transvaginal Pelvic Reconstructive Surgery

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**Abstract** Over the past decade, a huge number of new implants and ancillary devices have been introduced to the market. Most of these have become clinically available with little or no clinical data or research. This is a less-than-ideal situation, and this subgroup of the ad hoc IUGA roundtable conference wants to open the discussion to change this, by proposing a pragmatic minimum clearance track for new products being introduced to the market. It consists of an accurate and more standardized product description, data on the biological properties gathered in animal experiments, anatomical cadaveric studies, and upfront clinical studies followed by a compulsory registry on the first 1,000 patients implanted. Ideally, manufacturers should support well-designed prospective (randomized) clinical trials that can support the claimed benefits of the new product.

**Keywords** Graft · Mesh · Vaginal prolapse · Pelvic organ prolapse · Safety · Market · Implantable material · New product · Biological property · Prospective randomized trial

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## Introduction

In surgery for urinary incontinence, there has been an explosion of new implants and ancillary devices with a variety of different materials introduced to the market [1, 2]. Most of these have little or no data but are promoted and marketed very aggressively, at times on the back of products that do have data. The companies involved may be of the belief (no doubt supported by marketing data) that scientific data does not sell products. The perils of commercially driven surgical innovation have already been often stressed in our literature [3]. The potential dangers for patients as well as physicians have been highlighted and its ethics questioned, prompting a call for more stringent regulation [4, 5]. Such regulation may have advantages as well as disadvantages [6]. The primary concern is patient safety. Moreover, physicians consider it highly relevant that there is scientific evidence for innovative surgical techniques [7].

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We believe that the minimum standards *prior* to launch and marketing should be demanded ahead of a launch, and we suggest that these should include the following:

1. Comprehensive and exact data on the physical properties of the product.
2. Data on the biological properties of the product following implantation from high-quality animal studies.
3. Anatomical studies on cadavers.
4. A well-constructed cohort study.
5. Commitment to a compulsory registration of the first 1,000 consecutive patients after marketing clearance by the appropriate regulatory bodies.

This process would prevent companies avoiding doing experiments and clinical trials on the devices, by claiming substantial similarity to products already on the market [8]. The industry has so far argued successfully that the evidence required from drug trials is not necessary for devices. Consequently, the standards of clinical trial assessment are much lower for devices than for drugs [1].To that adds the limitation that it is difficult to patent operations in pelvic surgery. As a consequence, there is the rapid introduction of "me too" devices and operations with little or, in some cases, any evidence of the device having had any form of independent testing.

## Description of physical properties

To enable the comparison of the widening range of implants and ancillary devices used in pelvic floor surgery, it is important to describe them accurately, preferably in a standardized fashion. We see at present no reason to use a description of the physical and chemical characteristics of synthetic implants that is different from that used to describe implants used in hernia repair. We, therefore, recommend that manufacturers use the guidelines published by Cobb et al. in 2009 to describe their products [9]. These were agreed upon at the American Hernia Society Annual Meeting in 2007. This should be both for regulatory purposes as well for the product inserts for patients and physicians. If in the future additional variables are shown to be relevant to patient outcomes, amendments will then be made. Pelvic floor surgeons should, as end users, have knowledge of such a description system, as it will be their primary tool for comparing competing products. Using "the same language" will benefit all partners involved [9]. One may obviously criticize the clinical relevance of the individual parameters proposed below. Mainly that they have not been truly validated, but it seems to be sensible to describe accurately and in a standardized way what is being used clinically.

An ad hoc IUGA standardization committee in 2010 proposed the use of the term "implant" for synthetic meshes, whereas grafts are their biologic counterparts [10]. Meshes are essentially classified based upon (1) the *nature* of the material used, (2) its *fabrication process*, and (3) its *physical properties*. The additional terminology and testing conditions to describe the properties of materials describe in essence the deformation behavior of implants when subjected to a certain load. Many of the terms and concepts are borrowed from the textile industry and apply mainly to synthetic implants. Because many physicians are not that familiar with that type of terminology, we will highlight some essentials. The minimum variables to be reported are summarized in Table 1.

### *Fabrication process*

The filaments composing an implant are either knitted or woven. In *weaving*, one parallel set of filaments is aligned lengthwise in the direction of the fabrication (called the *warp* direction) and a second set of filaments is perpendicularly passed over and under the warp (called the *weft* direction). Woven fabrics have the same mechanical properties in both directions and are, in other words, isotropic. They are typically densely packed to avoid spreading apart from the constituting filaments when forces are applied perpendicular to the implant. *Knitting* means that a continuous filament or yarn is looped by a needle around another yarn (called the *weft*). During the process of knitting, different mechanical properties according to the warp or weft direction can be created. This induces anisotropy or directional variability. Over the years, the trend has been to more porous and flexible, lighter and less strong materials. The most frequently used *synthetic* polymers today are polypropylene (PP), polyvinylidene fluoride, and polylactic acid. Some implants are made of a mixture of different polymers, which may individually be either degradable or durable. These are in the form of fibers, films, or sheets and may be added for modulating the surgical handling or other physical properties. We anticipate the increased use of added coatings. Nanoparticles or microparticles, for instance, are used as markers or to deliver drugs locally [11, 12].

**Table 1** Required physical specifications of all products

| |
|---|
| Nature of the composing polymer(s) and filament(s) |
| Resistance of polymer(s) to degradation (permanent or resorbable) |
| Weaving type (knitted or woven) |
| Filament diameter |
| Pore dimensions and density |
| Exact dimensions and weight |
| Total surface area of all filaments in the graft to be implanted |
| Uniaxial tensile stress–strain plot, in the plane of and perpendicular to the material, determining |
| Tensile strength and stiffness |
| Distentional stiffness |
| Bending stiffness: flexural rigidity |

*Physical properties of materials*

The American Society for Testing and Materials (http://www.astm.org) specification D4850 determines the terminology to describe textile fabrics, which can also be applied to the description of implants. Because the terminology is often inaccurately used, we will describe the basics concepts used when describing a given material.

- Relative *weight* (also called density) is expressed per unit area (in grams per square meter) and is a measure of heft. For the latter, surface (in square meters) rather than volume (in cubic meters) is used because the thickness of the used fabrics is considered as negligible.
- *Load* should describe the force per unit width (in newtons per centimeter) where width stands for the dimension of the tested fabric perpendicular to the direction of the force applied. Such normalization allows the comparison of specimens of different sizes.
- *Dimension change* refers to changes in length or width, and dimensional stability refers to such dimensional changes under specific (mechanical, chemical, or biological) conditions. Contraction (also referred to as shrinkage) is just one example of dimensional stability, although this occurs in vivo.
- *Strength* is the maximum stress the material can handle prior to breaking or tearing. Experimentally, it is determined by measuring the maximum load required to tear a specimen of *a given geometry* apart. To allow the comparison of materials, results of such tests *should be* normalized to a standard width and be done under the same preconditioning.
- *Deformation* is a more general denominator for geometrical (shape or size) changes. Typical testing conditions involve pulling *the material* apart, inducing "strain." Most are familiar with uniaxial testing conditions. A pulling force is applied to a clamped specimen whereby "stress" expresses the magnitude of that force per unit area. It results in the elongation (strain) of the specimen, the latter quantified by the change in length divided by the original length and expressed as a percentage to the initial length.
- *Stiffness* is the ratio of a force applied on an elastic medium to the resulting deformation. Compliance is the inverse of stiffness. Stiffness is a very general term and can relate to several conditions whereby forces are applied. One well-known example is "tensile stiffness," relating to the deformation as a consequence of uniaxial loading in the longitudinal direction of the specimen. *Distentional* stiffness would be the same but for a load *perpendicular* to it. *Bending* stiffness in turn relates to flexing forces. Flexibility describes the ability of a material to be flexed or bent repeatedly. This can be measured in different ways, for instance, by sustaining its own weight or using a loaded cantilevered beam.

For completeness, *elasticity* is a descriptive term that is often confused with, however is not interchangeable with, stiffness or compliance. Elasticity describes the property of a material whereby it changes in shape and dimensions when subjected to forces and does or does not recover its original configuration after the removal of those forces. When it does not, the resulting permanent deformation is called plastic deformation.

We propose that the manufacturer provides the information displayed in Table 1. It starts with the nature of the product and an accurate description of its geometry as well as its physical properties (Fig. 1).

In hernia surgery, three characteristics are considered to be key for buttressing materials, which we propose to be the minimum data set to be included in the product insert [9]:

1. Tensile strength and stiffness in the plane of the specimen. Uniaxial loading in the plane of the material, with a standardized width, eventually determines uniaxial tensile *stiffness* and tensile *failure load*. The tested specimen should come from the central portion of the material used and is clamped over its entire width. This way, the edge of the material is not in the specimen as it may have different physical properties.
2. Strength and stiffness following distention *perpendicular* to the plane of the implant. One example is burst testing, which applies a standardized spherical load to the specimen clamped between standardized annular grips. The resistance to the load and the displacement of the load applicator determine the circular bending *or distentional stiffness*.
3. Flexural rigidity of an implant is determined by bending by extrusion or cantilever bending. In the former, the experimental setup measures load used by a blade or disk, and its displacement, as a piece of material is forced through a longitudinal slot (determining linear flexural rigidity or folding stiffness) or an annular opening. The cantilever test measures how a specimen bends under its own weight. The specimen is advanced along its longitudinal axis over the edge of the measuring device at a fixed speed, and the length at which the overhanging material contacts the underlying surface at a 41.5° angle is measured.

Some of the above terminology or biomechanical tests are also applicable to "explants," i.e., specimens retrieved from experimental or clinical subjects after integration by the host. *Biologically* derived materials are also used today. Overall, biologic grafts are acellular scaffolds which should facilitate the growth of host tissue. They are typically

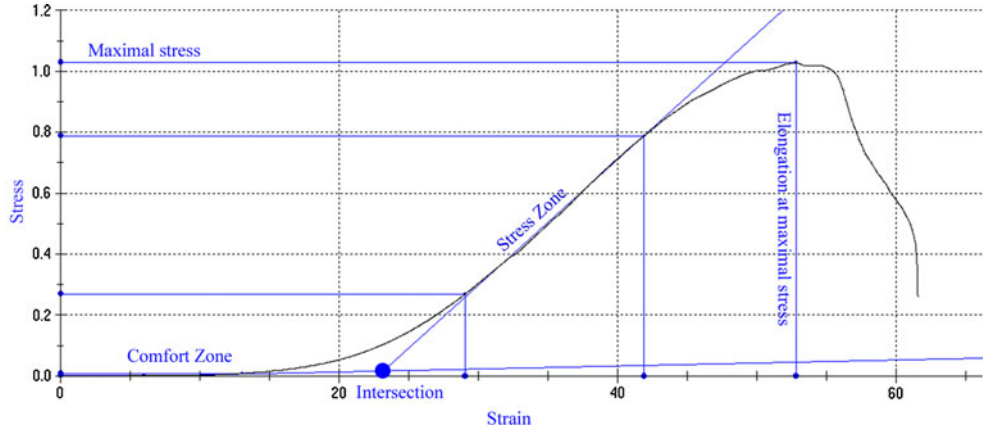


**Fig. 1** Outcome measurements at tensiometry. In the stress–strain curve, the comfort zone is limited to the physiological range of deformation, whereas the stress zone is in the range of supraphysiologic stress. The stiffness (in newtons per square centimeter) in both regions is given by the best-fit linear regression line. The transition between the comfort zone and the stress zone is determined by the intersection (in percent) of both regression lines. At maximal stress (in newtons per square millimeter), the maximal elongation is measured (in percent) (reprinted, with permission from [25])

derived from bovine pericardium, porcine or bovine dermis, porcine intestine, or even human dermis. Some are degradable, while others have been cross-linked to make them resistant to degradation. There is, to our knowledge, no standardized way of describing this group of materials. Also, in the future, we should foresee minimum requirements for cell-based products used in incontinence and pelvic organ prolapse (POP) surgery, which may also be used in combination matrices.

## Animal experiments

### *Purpose and design of animal models and experiments*

Experimental studies play a role in the better understanding of the host response to implants and may help anticipate failure or local adverse effects. In essence, animal models document the host response following implantation in a quantitative way under very well-controlled conditions. This is clinically impossible. Roughly spoken, experiments can be dedicated to study the immune response, wound healing response, or surgical conditions of use. Pathophysiologic models, on the other hand, may be more interesting to scientists trying to get a better understanding of disease as well as the evaluation of therapeutic or preventive measures.

We believe that experiments dedicated to documenting the incorporation of implants into the host are a minimum requirement. We refer to an earlier document of the first IUGA roundtable conference for further details on the nature of the host response as well as the experimental methods used [13]. Though there are certainly limitations for extrapolating findings to clinical use, it seems again cautious to screen materials in vivo so that major toxicity issues are ruled out as much as possible, as well as to document the in vivo behavior of the material being incorporated by the host. Many imbalances can occur in this process, including abnormal fluid accumulation, infection, folding, contraction, biochemical or architectural degradation, insufficient or exaggerated scarring, or extrusion. For materials used within the abdomen, adhesion formation may be an additional worry [14]. The relevance of these could be the occurrence of symptoms or need for reintervention [10]. Making such experiments compulsory should reduce the risk to patients, but also may be useful to the industry itself, in the objective assessment of claimed advantages of new products as well as in reducing the risk of being held responsible for adverse effects.

For the study of the integration of the material by the host, the material is usually implanted in the area of repair of a surgically induced trauma or defect. Prolapse surgery typically involves repair of fascial structures, and the bulk of the studies is being done in models that were borrowed, again, from hernia surgery [15–20]. In essence, they involve the repair of a fascial defect, either by primary sutured repair reinforced by the implant or by overlaying the defect. Scientists may be interested by additional experimental variables, such as contamination of the operative field with a given number of bacteria, the administration of hormones, antibiotics, growth or differentiation factors, or even cells, etc. [21–23]. Animals are followed up longitudinally for days to months, or even years, depending on the purpose of the study. Sacrifice takes place at given times, depending on the anticipated resistance of the material to degradation or the expected host response. At that moment, the implant, the interface, and the neighboring host tissue become available for further examination. In rats, usually only one full-thickness defect is created, which is repaired, and follow-up is typically limited to 180 days. Rabbits have a longer

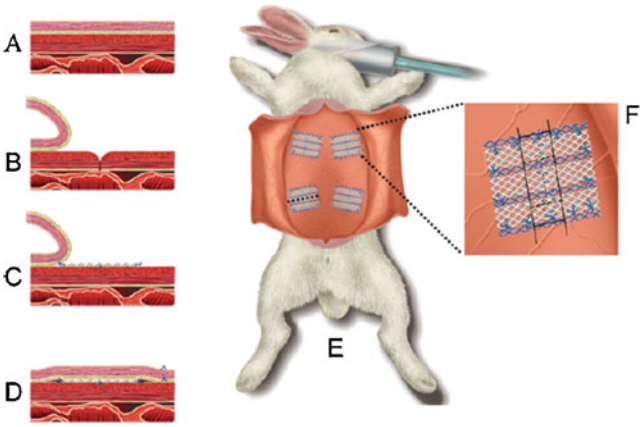


**Fig. 2** Experimental setup for primary repair of full-thickness abdominal wall repair using four implants in one rabbit. Cross-section of **a** intact anterior abdominal wall; **b** following preparation of skin flaps, creation of full-thickness incision; **c** primary repair of the defect and fixation of the implant; and **d** closure of the skin. **e** Magnification of the area in cross-section.. Reprinted with permission from Springer and the authors [25]

lifespan, allowing long-term follow-up studies. Their size also permits the creation of several defects in the same animal as well as the harvesting of larger tissue specimens (Figs. 2, and 3) [24, 25]. Rabbits are known to have a different collagen metabolism from man, which may have an impact on wound healing as well as degradation of acellular collagen matrices [26]. Also, there may be methodology issues with immunohistochemistry as well as molecular tests. Though primate experiments may be contemplated, there is an increasing public sensitivity of these experiments, leading to banning them virtually in Europe.

Findings from abdominal wall reconstruction models may not be simply extrapolated to outcomes after vaginal surgery. The vaginal microenvironment, anatomy, and wound healing response are definitely different from that in the abdominal cavity and wall [27, 28]. Size-wise, the lower limit of experimental vaginal surgery is the adult rabbit, whereas sheep may be a closer mimic to the clinical conditions of POP surgery. In rabbits, successful insertion of implants in the posterior vagina has been described, but grafted material is by definition small [27–33]. In contrast to abdominal repairs, rabbit vaginal repairs with mesh result in exposure rates as high as 50%, which is far above that reported clinically [30, 31, 34, 35]. It is, therefore, uncertain whether the mechanism that is driving extrusion in this model is similar to what is happening clinically. It may be related to the size of the implant used (42% exposure for a 2.9×0.8-cm implant versus 10% for a 2.0×0.8-cm implant) [34]. The overall small implant size in this model, together with a higher risk of exposure and the potential of contraction, may render biomechanical measurements unreliable, if not impossible [36].

The sheep model may, therefore, be more appropriate for evaluating implants used in vaginal surgery. Size-wise, it has been shown possible to implant as many as three (yet small) meshes through a midline incision, with an overall exposure rate of 25%, in particular in the anterior vaginal wall [37]. Good biomechanical experiments require large specimens so that only one implant may be used at a time. This obviously is associated to an increased experimental cost. Remarkably, the vagina of sheep is insensitive to strain rate in biomechanical testing [36]. Given the limited previous experience with the vaginal models, as well as the limitations on the implantable specimen size, it seems that, at this moment, we cannot enforce extensive experimentation on this higher species until the true added value is demonstrated.

Although animal experiments provide a great deal of information, they have their limitations. Most experimental studies use animals without the underlying condition (prolapse), nor do they have the predisposing risk factors or comorbidities that may influence wound healing (hormonal status, obesity, smoking, etc.). Virtually, all animals are models are (partly) quadrupeds, hence they also have a different pelvic floor musculature.

### *Outcome measures for the evaluation of experimental explants*

Typically, the implant and surrounding tissue is harvested at given time points. At that moment, the operation site is inspected for any gross signs of infection, herniation,

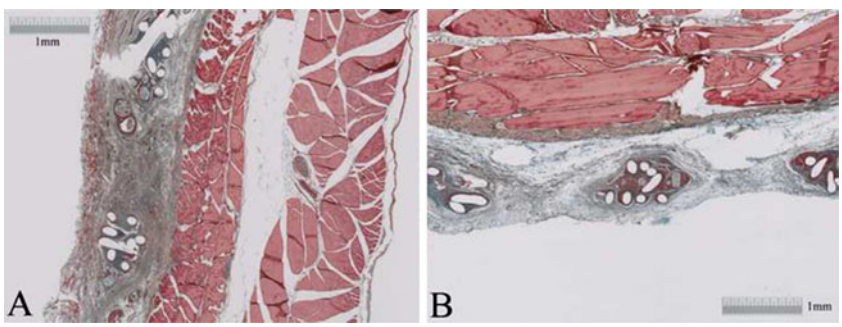


**Fig. 3** Histologic section of a PP-32 explant (Movat's stain). There are no quantitative techniques available to evaluate the presence of bridging fibrosis. We have come across areas of what looked as bridging fibrosis (**a**), whereas others do not have that feature (**b**). ruler: 1 mm. Reproduced with permission from [25]

folding, or migration. The explant dimensions are used to quantify eventual contraction. When biomechanical measures are the purpose of the experiment, sufficiently large specimens undergo physical testing. There are lots of methodological issues for doing this accurately, which were excellently reviewed by Abramowitch et al. [38]. Collaboration with a biomechanical engineer or department is recommended. Biomechanical experiments measure strength as well as the deformation behavior prior to breakage of the surgical construct. The former is usually not a cause of concern; the latter may be clinically most relevant. In vivo, the deformation of the implanted area can be measured with purpose-designed devices borrowed from dermatology [39–41]. An additional advantage is that such methods that do not require tissue harvesting allow for longitudinal studies. However, measurement devices purposely designed for experimental conditions are still lacking. Ex vivo, the active properties of explants, such as contractility, can be determined [42]. Imaging studies can theoretically document conformational changes during integration into the host, using either microultrasound, computerized tomography, or magnetic resonance imaging [11, 12]. It seems to us that, at this moment, these novel methods, yet promising, are too investigational to make them basic requirements for experimental evaluation prior to clinically launching a product.

At the time of explantation, part of the specimen also becomes available for structural analysis at a more detailed level. Using different staining methods, one can quantify the inflammatory response, eventually also using immunochemistry against cell-specific markers [18, 43]. The organization, composition, and amount of connective tissue can be scored [44, 45]. More advanced biochemical, immunohistochemical, or molecular testing can be done as well, for instance, to localize or quantify collagen and elastin subtypes, smooth muscle actin, hydroxyproline, or inflammatory markers. Electron microscopy can document degeneration of the fibers of the implant or for matrices cell ingrowth [46].

### *Recommendations for animal experimentation for new implants*

With the current knowledge, it seems to us that, for products that are based on polymers that have been used previously, the principal purpose of such experiments is to document the host inflammatory response accompanying the integration or resorption of the material. In our opinion, experimental data cannot be extrapolated from look-alike products. In other words, novel products need to undergo prior experimental testing with the product exactly as it will be taken to the market. More specifically, the exact fabric, sterilized and packed as for sale, and from one production lot must be used for these experiments. It is at the discretion of the investigators what species will be used, as there is no evidence that one species, location, or method of implantation is clinically more relevant than another. As to the experimental design, relevant reference groups must be included next to the investigational product. It seems fair to insist on at least six animals at each time point of evaluation, and typical time points for documentation of the host response would be 14, 30, and 90 days for permanent materials. The exact time points and duration of the experiment will obviously be adapted for materials that change over time. In summary, experiments need to be long enough to study degradability, as well the time it would take to reach a steady state in the host response. Outcome measures should include comprehensive documentation of any physical changes in the implant, wound healing problems, and histological documentation with quantification of the inflammatory response.

This protects patients, and at the same time, the medical industry can consider this preliminary experiment as an easy tool for risk assessment. A good example is the historical Mentor-Porges Incontinence “ObTape” sling. It was brought to the market without any convincing experimental (let alone clinical) data, based on a successful so-called 510K application to the FDA. Indeed, “ObTape” is made from monofilament PP, similar to the TVT (Gynecare, Ethicon, Sommerville, NJ, USA) sling. However, any similarities to other monofilament macroporous woven PP slings ended there. “ObTape” is a nonwoven mesh utilizing a thermal bonding process. Macroscopically, it resembles microporous Goretex (W.L. Gore, Flagstaff, AZ), which is known to have a high local complication rate. In an animal experiment, Slack et al. demonstrated a completely different inflammatory response when compared with the more openly constructed Sparc (AMS, Minnetonka, MI, USA) tape [47] (Fig. 4). The inflammatory response to Sparc subsided with time and was followed by fibrous tissue deposition, tissue integration, and new vessel formation. In contrast, the ObTape induced a chronic inflammatory response that increased with time. This prevented tissue incorporation, inducing a fibrous tissue capsule with a permanent foreign body reaction. In other studies using scanning electron microscopy, thermal damage to the fibers was demonstrated, which might increase the propensity of this tape to induce chronic inflammation. This coincided with numerous reports in the literature detailing the occurrence of exposure as well as infection and associated soft tissue injury [48, 49]. Appropriate animal studies prior to clinical implantation would, in our opinion, have suggested that the tape was either not suitable or at the very least prompted a limited observational human study before its introduction to the market. Eventually, the product was withdrawn from the market but was involved in a class action in the USA, which was resolved in favor of the plaintiffs.

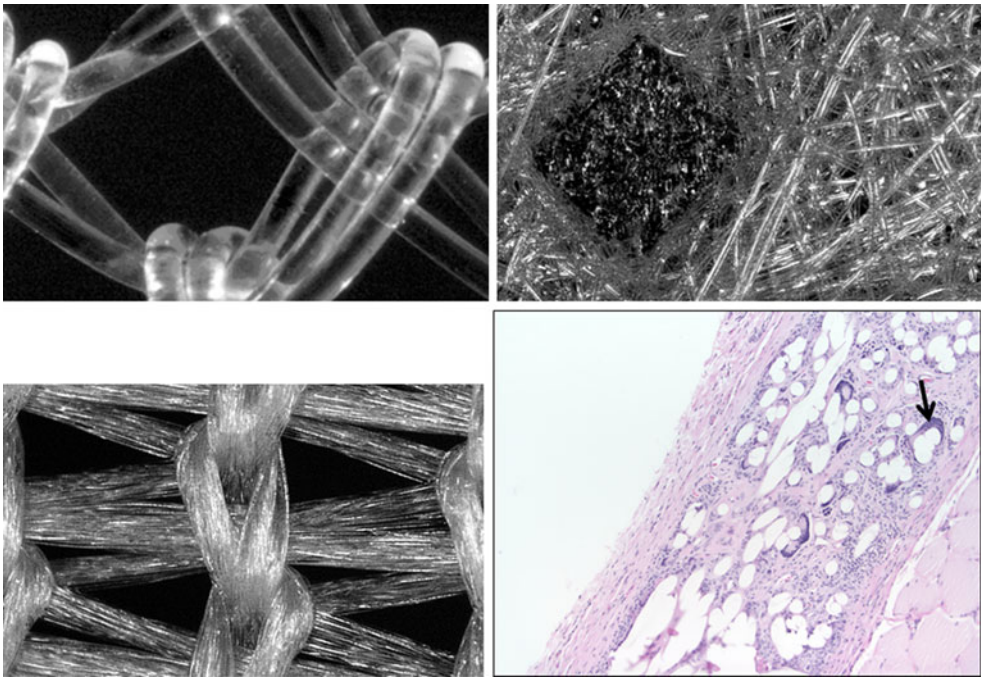

**Fig. 4** Comparison of a macroporous PP sling (Sparc, AMS, *top left*) to the multifilamentary IVS (Covedien, *bottom left*) and ObTape (Mentor-Porges). *Inset bottom right* explant from an ObTape, with areas of foreign body reaction (*arrow*) within an outspoken chronic inflammatory reaction. Filaments are the open areas [47]

That story is reminiscent of another sling. ProteGen (Boston Scientific Corporation, Natick, MA, USA) was a polyester woven sling, coated with pressure-injected bovine collagen and part of a Vesica sling kit that also contained bone anchors, which eventually ended up to be the combination of two unproven ideas [50]. The material used had "substantial equivalence" to other devices and got cleared, although prior to its marketing, it was never used clinically for urogynecologic indications. The company relied on clinical experience with the same fabric used for cardiovascular applications, which was called "Hemashield." There were 90-day animal data, although we have, at present, no knowledge on the exact details of these studies [3]. The product was cleared in April 1997, marketed in June of that year, and then recalled in January 1999 [51] because of an unexpectedly high exposure and dehiscence rate, leading to reintervention and several single and class action law suits [52]. Again, this product went from concept to a clinically marketed product without sufficient intermediate steps.

## Anatomical studies in cadavers

Anatomical studies also play an important role in the preclinical evaluation of new procedures. Vaginal prolapse surgery is often technically difficult because surgery is compromised by limited visual access. Many of the new operations using trocars to facilitate mesh placement are, by their nature, "blind" surgical maneuvers. In doing so, a surgeon may have to go through anatomical spaces with whom she or he is not familiar and which may contain potentially dangerous anatomical structures. Preclinical cadaver studies allow the assessment of correct placement or risk of potential injury by the technique and the relationship of the trocar passage as well as remaining implants to the surrounding structures to be explored. There is no way of calculating the number of cadavers needed for the study, but four seems to be a reasonable pragmatic minimum number, typically providing eight anatomical sites for nonmedial structures. The number should be logically adapted if the novel technique would have to take into account known anatomic variability of structures that are critical to the new procedure. The laws governing the access to and performance of surgery on cadavers will vary among countries. Ideally, most companies would commission anatomy departments that have experience in this type of study that will be able to walk the inventor through the process.

In order to facilitate a rapid and "lifelike" dissection, it is recommended that the cadavers be preserved with an ethanol–glycerol solution or fresh frozen. The purpose is to preserve tissue plasticity and allow for the corpse to be positioned similar to the actual procedure (i.e., with the limbs in the lithotomy position). The dissection should be undertaken with the appropriate instruments and operating tables so that it is as lifelike as possible, according to the technique set out in the manufacturer's "instruction for use" brochure. Ideally, the inventor should clearly describe the required dissections.

For techniques that use trocars in the pelvis, a groin dissection is needed as well as a pelvic dissection. The groin dissection should be done along the route of the trocar. A trocar can be left in position to facilitate accurate identification of the route. Obviously, if a strap of mesh has been left in place, it will perform the same role. After surgery, a laparotomy is performed to evaluate the anatomical position

of the implant(s) involved. This will allow the retropubic and retroperitoneal spaces to be dissected and help identify possible anatomical complications.

Considering how many new procedures have arisen, there is a paucity of papers reviewing the anatomical aspect of these procedures. For instance, the relevance of such studies has been demonstrated for incontinence procedures [53–55]. Also, for prolapse surgery, Reisenauer et al. demonstrated the relationship of the PROLIFT mesh (Ethicon, Sommerville, NJ, USA) and the neighboring neurovascular structures, to name only a few [56, 57].

## Clinical trials

Randomized controlled trials are hailed as the highest level of evidence. For instance, the TVT procedure certainly became broadly accepted because of the availability of convincing data from a randomized trial, comparing it to the then present standard of care [58]. Given that industry would sponsor such trials, these types of results are ultimately a good return on investment from a commercial viewpoint. When conceiving such a trial, the independency of the investigators to the sponsor of the study needs to be carefully contracted.

However, here are several reasons why the ideal clinical trial approach has not yet materialized. From the device industry's viewpoint, the first reason is obviously that it is not required. Second, their current economic model is based on short-term market share objectives and immediate return. Although patenting may protect innovators to a certain extent, competitors quickly introduce look-alike products, which in turn provoke the fast turnover typical to this sector, claiming advantages that are usually unproven if not at all questionable. This is obviously less than ideal.

Breaking with this will certainly come at a price: initially for the industry, but eventually this will impact the end user as well. It may slow down innovation and definitely may increase the price of products [6]. It is clear that such ideal surgical trials, where differences between treatments are likely to be moderate or small, will come at a substantial cost. But even if such randomized trials would ultimately show advantages of one treatment over another, they would likely fail in identifying uncommon complications. Add to that the common problems associated with randomization and recruitment [59].

We, therefore, believe that a more pragmatic approach could be recommended as a less-than-ideal, yet absolutely required and realistically doable first step. We would propose that the prospective multicenter cohort study is an absolute minimum for the registration process prior to marketing. As per the example below, such a multicenter cohort study would include 118 patients with a minimum follow-up of 12 months, as will be explained below. This approach will yield a minimum of safety and efficacy data. Obviously, sample size might obviously need to be adjusted according to the primary outcome measure chosen in another example.

### *Example of a protocol and time line for the introduction of a novel device in the treatment of POP*

*Cadaveric training and device run-in* In preparation of a multicenter study, all future surgeons would first need to be trained on cadavers and then complete the procedure on device run-in (DRI) subjects under the supervision, and to the satisfaction, of a clinical observer prior to enrolling study subjects in the formal trial.

In a prolapse study, one-sided 97.6% confidence intervals (CI) will be estimated for recurrence of POP-Q (defined as greater than or equal to stage II or surgical reintervention). The criterion for success will be that the upper 97.6% one-tailed CI will not exceed 20%. With 118 evaluable subjects, there need to be 15 or less recurrences for the 97.6% upper CI to fall at or below 20% using exact binomial confidence limits. Patients should be evaluated presurgically, during surgery, prior to discharge, at 4–6 weeks, and then at 6 and 12 months.

This structure will lead to four main analysis sets:

1. The *training analysis set* includes only DRI subjects.
2. The *safety set* will contain all subjects who receive treatment. This should include all DRI subjects and will be used for some effectiveness summaries as well as for all safety studies.
3. The full analysis set will contain all treated subjects, except DRI subjects (i.e., the intent-to-treat set).
4. The per-protocol set includes all subjects without major protocol violations who complete the 12-month follow-up or rare failures at any time up to withdrawal.

### *Primary and secondary effectiveness variables/criteria*

Anatomical outcome by POP-Q will be the *primary outcome variable*. Usually, success will be a POP-Q score of ICS stage $\leq 1$ in all treated compartments.

Secondary variables will depend on the procedure but should include data from:

1. Mean scores and change from baseline of quality of life tools at 6 and 12 months. These should include tools to evaluate prolapse, urinary, bowel, and sexual function.
2. Summary of POP-Q at 6 and 12 months.
3. Success at 12 months.
4. Date of return to normal activities.
5. Incidence of new-onset dyspareunia, vaginal, urinary or bowel problems, reintervention.
6. Time in the operating room.
7. Length of procedure.
8. Length of hospitalization.

9. The 24-h postoperative pain scores, and then at the 4- to 6-week visit.
10. Comparison of POP-Q scores in DRI versus non-DRI subjects.

*Methods of analysis*

Because it is a single-arm study, output should be limited to descriptive statistics (mean, standard deviation, minimum, median, maximum, and 95% CI for continuous data and number, percent for discrete data). It is a good idea to do an exploratory analysis to compare the results in the DRI versus non-DRI subjects. A Cochran–Mantel–Haenszel test can be used for this. Time to events can be analyzed using Kaplan–Meier methods.

*Safety*

All adverse events (AEs) will be included in the safety set. These can be classified as mild, moderate, or severe. Mild is defined as the awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient. Moderate is defined as interference with the subject's usual activity, although not precluding it. Severe events are incapacitating, with the inability to perform the subject's usual activity. Other serious adverse events (SAEs) for (POP) surgery include:

1. Death, any life-threatening event, permanent impairment of a body structure or function, prolongation of hospitalization, or medical or surgical intervention to prevent permanent intervention [60].
2. Inability to work or perform usual activity.

AEs must be monitored continually; each AE must be reviewed by the principal investigator and preferably a data monitoring chair to agree on the type of AE and appropriate action to be taken. SAEs or suspected unexpected serious adverse reactions must be reported to the Medical Research Ethics Committee and Medicines and Healthcare Products Regulatory Agency within 7 or 15 days. The above recommendation is taken from the current European Clinical Trial Directive Legislation, which currently applies to investigational medicinal products [61]. An IMP is a pharmaceutical form of an active substance or placebo being tested, or to be tested, as a reference in a clinical trial. Strictly speaking, trials with surgical devices are in a gray area, but it is the expectation that, eventually, the above standard will also apply since patient safety and scientific robustness is important in any clinical trial [62].

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the declaration of Helsinki, principles of Good Clinical Practice, and eventually other locally applicable regulatory requirements. Investigators may only begin recruitment after full approval of the protocol and adjunctive material has been obtained from the local ethics committee or the institutional review board.

Post-marketing surveillance study for product safety and comparative clinical trials

The above steps may not take an unreasonable time (Table 2) but would have to precede marketing. Post-market surveillance covers any monitoring activities which include the vigilance system for medical devices in use. In Europe, vigilance describes the manufacturers' responsibility to inform the responsible government authority of any adverse incidents as proscribed in local laws. This includes mechanisms for implant registration, distribution records, recall procedures, and complaint handling [63]. Such safety data is very important for an overall assessment of the mesh product/procedure to detect *unanticipated* AEs. Indeed, a small, 118-person study as above will fail to identify events that, for example, occur with a frequency of <1%. In order to overcome this problem, we believe that the company should agree to setting up a registry for the first 1,000 patients to undergo the procedure and commit to publish or make public the results. Scientific bodies could agree to publish such registries as long as they meet certain minimal standards. Physicians starting new procedures should agree to participate until the number has been reached. Registries would give an early indication of possible problems and direct further and better studies. They may also overcome limitations encountered by the current system of voluntary reporting using, for instance, the MAUDE database.

This group recommends that a registry be established for all implanted products for a minimum of 1,000 patients and for a minimum of 12 months to monitor the occurrence of such unanticipated as well as rare AEs. During that period, all patients would have the implantation of a mesh product from the same lot number and no alterations in the morphology of the mesh during the conduct of these studies would be allowed. That registry does not exclude the spontaneous reporting at a later stage, such as the "yellow card" registration for pharmaceutical agents currently in practice.

If such a registry had been established, in the case of the transobturator ObTape® or of the ProtoGen® sling, the high rate of exposures, serious infections, and pain issues would have come to light quite early after the initiation and before general use by surgeons. An early warning would have avoided the disastrous results of using these products by unsuspecting physicians. In the absence of such a registry (and appropriate action by the authorities and/or industry), one has to wait for publications reporting a higher than expected incidence of these events, which by definition will

**Table 2** Anticipated time line of the current proposal for the introduction of novel devices into the market

| Steps | Goals | Time line |
|---|---|---|
| Pre-marketing, nonclinical | | |
| 1. Preclinical file | Accurate description of product—toxicity studies for new polymers | 0–6 months |
| 2. Preclinical testing—animal | Host inflammatory response | 0–12 months |
| 3. Cadaveric studies | Anatomical documentation | 6–12 months |
| Pre-marketing, clinical | | |
| 4. Clinical studies: phase II trial | Efficacy study | 12–24 months |
| | Long-term safety | Ongoing |
| Post-marketing | | |
| 5. Clinical studies: temporary registry | Surveillance study ($n$=1,000) | 30–42 months |
| "Yellow card"—MAUDE reporting? | Self-reporting on a larger scale | Ongoing |
| Recommended: RCT | Should prove whether product/procedure is advantageous/competitive | Should be conceived as early as possible |

be published later than the initial first 12 months of use [64–66]. Early detection would have prevented the substantial morbidity from the uncontrolled use of this product.

Because voluntary registries have the shortcoming of underreporting, it seems preferable that the registry would need to be comprehensive and mandatory. The satisfaction of both criteria is mandatory for the accumulation of meaningful information. Reporting forms must be designed in a manner similar to the case records of any well-designed study to completely encompass all known possible complications, with additional events added for those unexpected issues that may arise.

Further, this group recommends that a randomized clinical trial be initiated in order to substantiate and validate any and all claims that a product may make through its marketing. For example, these claims may encompass various advertised hypotheses, such as, this product produces less exposures or less mesh contracture, is easier to perform, or has a better success rate, to name a few. It is recognized that this will probably lead to comparisons between similar products, rather than to native tissue repairs. However, incorporation of the latter where appropriate is encouraged. Such studies would either parallel the above scenario or could be initiated after product registration.

The above scenario is a very generic one, which may not necessarily be compatible with what is currently the regulation in individual countries. There are indeed large regulatory differences between individual countries or continents (reviewed in [67] and [62]). The above may need to be adapted to local needs. It is also a first proposal to regulate this process that should prompt the discussion between regulatory bodies, physicians, and potentially patient organizations, as well as the medical industry. The proposal puts the responsibility on the manufacturers, to invest in gathering evidence, as well as physicians, who will have to participate in clinical trials or await their results prior to adoption of a novel technique [7].

## Summary

While this approach is not the highest level of study preferable, it would markedly improve the level of research currently in use when launching new products. It would also mean that new products could no longer be brought to the market prematurely without documented experience or evidence of efficacy. Any similar or look-alike product would inherently have to go through the same procedure. Meanwhile, the medical community needs to reject the use of products with no evidence to support them, irrespective of the price difference, as random introduction could lead to wide-scale medical disasters.

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